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Hair dyes and risk of glioma among Nebraska women

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Abstract

The etiology of brain cancer is not well understood. We conducted a population-based case–control study among 112 white women in Nebraska who were newly diagnosed with glioma between July 1988 and June 1993, and 215 controls, to identify risk factors for this disease. A 1.7-fold increased risk of glioma was observed for women who ever used hair coloring products (95% confidence interval (CI) = 1.0–2.9, 62 cases), and a 2.4-fold risk for those who used permanent hair coloring products (odds ratio (OR) = 2.4, 95% CI = 1.3–4.5, 39 cases). For women with the most aggressive form of glioma, glioblastoma multiforme, risk increased with duration of exposure to 4.9 (95% CI = 1.6–15.7, 10 cases) after 21 or more years of permanent hair coloring use. Higher risks were observed with earlier age at first use, but we did not see an exposure-response pattern with frequency of use of permanent dyes. No association was observed with use of non-permanent (sometimes called temporary or semi-permanent) hair coloring products. These suggestive findings need confirmation in future studies with larger sample sizes, fewer proxy respondents, and the ability to evaluate the effect of changes in formulations over time.

Introduction

Gliomas constitute over 90% of malignant cancers of the brain and central nervous system (CNS). The incidence and mortality from brain cancer have been increasing over the last several decades, especially in older adults [1]. Although much of this increase is thought to be due to changes in diagnosis and classification, neither the reasons for the increase nor the causes of brain cancer are well understood. The only known risk factor in humans is ionizing radiation; other factors associated with an increased risk of brain cancer include occupational exposures, such as organic solvents, electromagnetic fields, and vinyl chloride, as well as dietary and familial factors [1].

We conducted a case–control study in Nebraska to evaluate potential risk factors for this disease, including hair coloring product use. Previous studies have suggested that employment as a hairdresser or cosmetologist [2, 3] was associated with increased risk of brain and CNS cancer. Hair dyes have been suggested as the most plausible causal agents to explain excess of glioma and other cancers among hairdressers [4]. A case–control study in Canada found elevated risk for glioma among 'users of hair dyes or hair sprays' [5]. Therefore, we evaluated the role of hair coloring products in the etiology of brain cancer among Nebraska women.

Methods

Cases

Eligible cases were white residents of 66 eastern Nebraska counties, age 21 years or older, newly diagnosed with glioma (ICD-O codes 938–948) between 1 July 1988, and 30 June 1993. Cases from 1988 through 1990 were identified from the Nebraska Cancer Registry. Cases from 1991 through 1993 were too recent for inclusion in the Registry, and were identified by per

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sonnel at 11 hospitals in Lincoln and Omaha. Based on data from the Nebraska Cancer Registry for 1987–1988, 96% of the brain cancer cases and 94% of the gliomas from the 66 eastern counties of Nebraska were treated at those hospitals. Men were not included in the hair coloring product portion of the study because of the low prevalence of product use among male controls in an earlier study in Nebraska [6]. Cases were limited to whites to match the characteristics of the controls, who were selected from an earlier study, which excluded other ethnic groups because of expected small numbers. At the same time of enrollment of glioma cases, a series of stomach and esophageal cancer cases were also enrolled.

To insure that we captured all gliomas, we requested records for adult primary brain cancers (ICD-O Topology codes 191–191.9) from the Registry and participating hospitals. From the Registry, we also requested any records coded as gliomas (ICD-O Morphology codes 938–948.1), pineal tumors (codes 936), gangliogliomas (code 950.5), neurocytomas (950.6), and neuroblastomas from other and unspecified parts of the nervous system (ICD-O Morphology code 950.0 and Topology code 192).

Cases were reviewed by a neuropathologist (RDM) to identify eligible cases (only gliomas) and to determine the histological subtype [7]. A total of 168 potential female cases were identified for the study (81 from the Nebraska Cancer Registry and 87 from the 11 hospitals). Of these, 31 cases had insufficient material for pathology review (n = 12) or were determined not to be gliomas in the pathology review (n = 19).

Controls

As described previously [8], controls were randomly selected from the control group of a previous case–control study of non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and chronic lymphocytic leukemia conducted in 1983 to 1987 in the same geographic area [6]. In that study (hereafter referred to as the lymphoma study), population controls were frequency matched to the hematopoietic tumor cases by their expected gender, race, vital status, and age (within five years) distribution in a 3:1 ratio. Controls under the age of 65 were drawn at random from the general population of eastern Nebraska (in 1985 to 1986) using random digit dialing. Subjects over age 65 were identified from the Health Care Finance Administration (HCFA) (Medicare) files. Controls for deceased cases were selected from Nebraska mortality records with an additional matching criterion of year-of-death (in 1983 to 1986).

In the current study, the controls were frequency matched to the expected gender/year of birth distribution of the glioma, esophageal, and stomach cancer series. Deceased cases and controls were not matched on year of death. For the youngest cases, we had insufficient numbers of controls; therefore, new controls born in 1967 to 1971 were identified from death certificates (n = 20, deaths in 1988 to 1993) and from random digit dialing (n = 3) by the same methods as in the earlier study [6]. We over-sampled living controls to provide more power for analyses by respondent type. Cases and controls who did not reside in eastern Nebraska at any time during 1983 to 1986 were excluded from the analyses.

Participation rates

We obtained permission to contact cases or their next-of-kin from the physician listed on the cancer registry or hospital record. Of the 137 female cases still eligible after pathology review, interview data were successfully obtained for 120(88%). Eight were subsequently determined to be ineligible (based on the interview data) due to residence outside of Nebraska during the entire study period, leaving 112 cases for analysis. Due to the severity of the disease, interviews were conducted with the next-of-kin or proxies for 88(79%) cases. The large majority of proxy respondents were either the spouse (44%) or other first degree relatives (48%). Of the eligible interviewed cases, 87% were astrocytic (52% of all cases were glioblastoma multiforme), 8% were oligodendrogliomas, 3% mixed gliomas, 1% ependymomas (n = 1), and 2% other unspecified gliomas. The two female cases with unspecified glioma had either oligodendrogliomas, astrocytomas, or mixed oligoastrocytomas, but could not be subclassified specifically into one of these groups due to the limited nature of the specimen.

Reasons for non-interview of cases included non-response or refusal by the physician (n = 4), refusal by subject or next-of-kin (n = 5), or inability to locate respondent, unlisted telephone number, or no answer at telephone number (n = 8).

Of 266 eligible female controls, 218(82%) (or their next-of-kin) were successfully interviewed. Three female controls were excluded after interview due to subject's reported previous diagnosis with brain tumor, leaving 215 controls, 97 living (44%) and 118 deceased. Reasons for non-interview of controls included refusal by subject or next-of-kin (n = 25), or inability to locate respondent (n = 21) and other reasons (n = 2). The overall control response rate was 73% (obtained by multiplying the response rates for the current reinterview (82%) by the original response rates from the lymphoma study, accounting for the household census response rate of 91%,

interview rates of 94% in the random digit dialing portion of that study, and response rates of 84% for HCFA controls and 82% for next-of-kin of deceased controls [6]).

Interviews

The brain cancer cases and the controls and/or their next-of-kin were contacted by letter, then telephone, and interviewed by telephone during 1992 to 1994. The mean, median, and maximum times between diagnosis and interview for the cases or their next-of-kin were 2.48, 2.53, and 5.42 years, respectively. The interview followed a standardized questionnaire. Questions were about exposures before 1985, so as to cover the same time period as in the lymphoma study. The questionnaire ascertained information on agricultural exposures, non-farming use of pesticides, a complete occupational history, residential history and water source, tobacco and alcohol use, diet, medical and familial cancer history, and, for women only, use of hair dyes. For hair coloring, questions included whether the study subject had ever used products that changed hair color gradually (e.g., 'Lady Grecian'), temporary or semi-permanent hair coloring products, or permanent hair coloring products. Duration, frequency, and age of first use and usual color used were ascertained.

Analyses

Maximum likelihood estimates of the odds ratio (OR) and confidence intervals (CI) were calculated using methods described by Gart [9]. The matching variables of year of birth and gender were controlled for in analyses, as was education. Logistic regression was used to evaluate effects of multiple factors simultaneously [10]. Adjustment for year of birth in finer categories, marital status, history of living or working on a farm, or dietary factors [8] did not alter odds ratios appreciably so results presented here are adjusted only for year of birth in four categories (<1915, 1915–1924, 1925–1939, 1940+) and education (less than high school; completed high school or vocational/technical/business school; some college or higher education).

Results

Use of any hair coloring product was associated with a 1.7-fold risk of glioma (95% CI = 1.0–2.9, 62 cases) (Table 1). Risks were elevated for the histologic subsets of astrocytic brain cancers OR = 1.8, 95% CI = 1.04–3.1, 56 cases), particularly glioblastoma multiforme (GBM, grade 4 astrocytic tumors: OR = 2.3, 95% CI = 1.2–4.3, 41 cases) (Table 1). Throughout the more detailed analyses described below, risks observed for all gliomas combined were due primarily or entirely to elevated risks for GBM.

Use of gradual hair coloring products was associated with statistically non-significant risk of about the same magnitude for all gliomas and for GBM as for any hair dye use (Table 1). Only five women with glioma reported using these products, risks did not appear to increase with duration of use nor with younger age at first use (not shown).

No association was observed with use of non-permanent (temporary or semi-permanent) hair coloring products, nor were there any gradients with duration of use, age first used (not shown), nor frequency of use (Table 1). No clear pattern was evident by color of non-permanent dyes.

Use of permanent hair coloring products was associated with a significant 2.4-fold risk of glioma and a 3.5-fold risk for GBM (Table 1). Risks increased significantly with the duration of permanent hair dye use among women with GBM and with all gliomas, but were inconsistent for all gliomas. Risks for both glioma and GBM were highest among women who began use in their thirties, and for women who first used permanent hair dyes before 1980. We did not observe increasing risk of glioma overall or GBM with increasing frequency of use. The darker (brown or brunette) shades of permanent hair dyes were associated with higher risks in both gliomas and GBM (Table 1). Only one case (a GBM) and no controls 'usually used' black permanent hair dye.

The combination of darker color and longer use was particularly strongly associated with GBM (Table 2). Risks rose to nearly nine-fold among women with GBM who usually used permanent black or brown hair dyes for 21 or more years. Risk of GBM was highest among women who used permanent dyes five or fewer times per year for 21 or more years (Table 2), rather than in the category of frequent use of long duration, where the highest risks would be expected. No association was observed among other gliomas (not shown).

No association was observed between gliomas other than GBM and hair coloring products, neither overall (OR = 1.1, 95% CI 0.5–2.4) nor for the three types of hair coloring products (gradual: OR = 0.6; non-permanent: OR = 0.6; permanent: OR = 1.2). No gradients were observed with any measures of exposure such as duration, frequency, or age first used (not shown).

GBM is the most aggressive of the gliomas, and most cases died before we were able to interview them. Among the four women with GBM who survived to be interviewed directly, three used permanent hair coloring

Table 1. Risk of glioma according to use of hair coloring products among women in Nebraska, 1988–1993[a]

Use of hair coloring products	Controls	All gliomas			Glioblastoma multiforme		
		Ca	OR	95% CI	Ca	OR	95% CI
Never any[b]	118	47	1.0		23	1.0	
Ever any	87	62	1.7	1.0–2.9	41	2.3	1.2–4.3
Ever gradual	8	5	1.7	0.4–6.6	4	2.7	0.6–11.7
Ever non-permanent hair dyes	55	22	1.0	0.5–1.9	15	1.3	0.6–2.9
Years used							
<1–10	20	7	0.8	0.3–2.3	3	0.7	0.1–2.9
11–20	11	5	0.9	0.3–3.4	4	1.5	0.3–6.1
21+	18	5	0.6	0.2–1.9	5	1.1	0.3–3.9
Times per year used							
<1–11	24	5	0.5	0.1–1.5	5	1.0	0.3–3.1
12+	25	12	1.2	0.5–2.8	6	1.1	0.3–3.3
Color 'usually used'							
Black	2	2	3.2	0.2–48.7	0	–	
Brown/brunette	29	11	0.9	0.4–2.2	7	1.1	0.4–3.2
Blonde	9	8	1.9	0.6–5.9	7	3.4	1.0–11.8
Red	1	1	2.0	0.0–78.1	1	4.2	0.1–182.1
Other	14	0	–	–	0	–	
Ever permanent hair dyes	40	39	2.4	1.3–4.5	27	3.5	1.7–7.3
Years used							
<1–10	13	10	1.9	0.7–5.1	4	1.5	0.4–5.8
11–20	13	7	1.2	0.4–3.7	6	2.3	0.6–7.8
21+	10	11	2.6	0.9–7.6	10	4.9	1.6–15.7
Trend test			1.91 $p = 0.03$			3.20 $p = 0.001$	
Age first used							
15–30	17	12	1.8	0.6–4.9	8	6.0	1.4–28.8
31–40	7	8	3.2	0.7–14.6	6	7.6	1.3–52.8
41+	12	8	1.7	0.5–5.6	6	1.8	0.4–7.7
Year first used							
1980 or later	5	3	1.3	0.3–5.8	1	1.6	0.1–18.5
Before 1980	31	25	1.8	0.9–3.4	19	3.0	1.3–6.7
Times per year used							
<1–3	14	9	1.7	0.6–5.1	7	5.3	1.2–24.1
4–6	10	11	2.9	0.9–9.9	9	9.4	1.9–51.1
7+	8	8	2.3	0.7–8.2	4	2.6	0.4–15.5
Trend			2.10 $p = 0.02$			2.85 $p = 0.002$	
Color 'usually' used							
Black	0	1	∞	–	1	∞	–
Brown/brunette	12	19	4.4	1.7–11.4	13	6.5	2.2–19.6
Blonde	18	12	1.5	0.6–3.6	8	2.1	0.7–6.0
Red	4	1	0.6	0.0–6.2	1	1.2	0.0–13.3
Other [c]	6	6	3.0	0.7–12.4	4	3.7	0.7–18.6

[a] Controlling for year of birth (<1915, 1915–1924, 1925–1939, 1940+) and education (less than high school graduate; completed high school and/or vocational/technical/business school; some college or higher education).

[b] Referent group

[c] 'Other' colors reported for cases were 'silver white,' 'ash blonde with brunette,' ''reddish blond,' 'all colors,' and 'blue-gray,'; for controls other included 'highlights,' 'gray frost,' 'auburn,' ''gray and white,' 'light ash brown,' and 'golden brown.'

products (OR = 6.4, 95% CI = 0.5–74.0). All three used them for 21 or more years (OR = 29.6, 95% CI = 1.6–2072.3), began before age 40 (OR = 8.1, 95% CI = 0.6–289.2), and used permanent hair dyes four or more times per year (OR = 15.2, 95% CI = 1.0–505.93), but risk did not increase monotonically with frequency. Elevated risks for darker permanent hair dyes were based on cases with next-of-kin respondents, while the three directly interviewed cases reported 'usually' using blonde permanent hair dye.

Dividing the deceased cases between those for whom the husband was the respondent and those for whom other relatives provided information resulted in fairly small numbers in many exposure categories and results

Table 2. Risk of glioblastoma multiforme by duration and frequency of permanent hair coloring product use and color usually used among women in Nebraska, 1988–1993[a]

Duration	Glioblastoma multiforme							
	Other colors[c]				Dark colors[d]			
	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI
Never used[b]	23	118	1.0					
< 1–20 years	4	20	1.0	0.3–3.6	6	6	4.9	1.2–21.0
21 + years	5	7	3.4	0.8–14.0	5	3	8.7	1.4–60.4
	<1–5/year				6 + /year			
< 1–20 years	3	14	1.4	0.3–6.9	5	9	2.9	0.7–11.7
21 + years	7	3	16.1	2.6–124.4	2	5	2.2	0.2–16.0

[a] Controlling for year of birth (< 1915, 1915–1924, 1925–1939, 1940 +) and education (less than high school graduate; completed high school and/or vocational/technical/business school; some college or higher education).
[b] Referent group.
[c] Blonde, red, and other.
[d] Brown/brunette, and black.

were inconclusive. Use of permanent hair coloring products was associated with GBM more strongly when the husband was the respondent (husband: OR = 10.2, 95% CI = 1.9–54.6, 12 cases; other: OR = 2.5, 95% CI = 0.9–7.1, 12 cases). Eleven of twelve husbands responded 'Don't know' for duration of use. Risks with early age at first use and with darker dyes were stronger for cases whose husband provided information than those for whom other relatives were respondents (not shown).

Discussion

This study provides some evidence of an association of permanent hair dyes and gliomas, particularly GBM. The association with GBM is relatively strong and supported by an increasing trend with duration of use. Higher risks were seen among women who were under age 40 at first use, although the relationship with earlier use was not monotonic. Frequency of use of permanent dyes did not show an exposure-response pattern. Darker dyes appeared to be associated with higher risks among cases with next-of-kin respondents. The subset of women with GBM who were interviewed directly was too small to draw firm conclusions; however, they tended to report patterns of hair dye use similar to those of all women with GBM.

The study was population-based, incorporated rigorous review of pathologic materials and classification of gliomas by histologic subtype, had high response rates for cases and controls or their proxies, and utilized a standardized questionnaire by trained interviewers who were unaware of subjects' case or control status. These strengths and some aspects of the results suggest that the results are unlikely to be due entirely to exposure misclassification. Risks were not elevated for all subtypes of gliomas, but only for the GBMs (risk elevations for all gliomas combined were due to increased risks among GBM). Risks were elevated only for permanent hair dyes, not for gradual or non-permanent hair coloring products. If the associations were the result of reporting bias, we would expect that risks would be elevated for all gliomas rather than a specific subtype and for all or most types of hair dyes. Risks were higher and exposure-response trends were stronger among directly-interviewed GBM cases than among cases with proxy respondents for nearly all measures of exposure. Finally, the pattern of associations with GBM – with longer duration and earlier age at first use of permanent hair coloring products – seemed more consistent than could easily be accounted for by overreporting among cases or their next-of-kin.

Chance, however, could explain a statistically significant relationship observed in a subgroup: here of permanent dyes with GBM only, particularly for those comparisons based on small numbers of exposed subjects. The strength of the association and the patterns of greater risk with duration and early age at first use argue against, but do not eliminate, chance as an explanation.

In addition, poor survival for brain cancer limited our ability to speak directly with many cases. We have assumed that proxies can reliably report ever use of hair coloring products and color of the product used, and are likely to be less accurate in reporting frequency and duration of use, but we know of no published

Table 3. Risk of brain tumors in studies of potential occupational exposure to or personal use of hair coloring products

Author (Reference)	Design	Population	Outcome	Exposure definition	Results
Personal use					
Ahlbom [11]	Case–control	78 Swedish men and women cases diagnosed in 1980–1981; 197 hospital and 92 population controls	Astrocytic brain tumors	Hair dyeing	OR = 1.5 (0.6–3.7) compared to population controls
Burch [5]	Case–control	215 cases in Toronto and southern Ontario adults diagnosed 1977–1981; 215 hospital controls	Gliomas	Ever used hair dye or hair spray	OR = 1.96 (43/22 discordant pairs)
Thun [12]	Cohort	573,369 women in ACS cohort	Brain and CNS	Permanent hair dye duration 1–9 years 10–19 years 20+ years	RR = 0.9 (0.7–1.1) RR = 1.1 (0.8–1.5) 0.7 (0.5–1.1) 0.6 (0.3–1.0)
Occupational					
Petersen [13]	PMR	~199,000 deceased white male residents of California 1959–1961	Brain cancer	Occupation of barber on death certificate	PMR = 131 (4 Obs/3 Exp) for ages 20–64
Milham [14]	PMR	429,926 deceased men, 1950–1979, and 25,066 women 1974–1979, Washington State	Brain and nervous system	Occupation of hairdresser or cosmetologist on death certificate	PMR men = 200 (2 Obs/1 Exp) PMR women = 50 (2 Obs/4 Exp)
Teta [2]	Cohort	11,845 female and 1805 male cosmetologists in Connecticut	Brain and CNS cancer	Cosmetologists holding licenses 5+ years and began hairdressing school <1966	SIR women = 168 (96–273), 16 cases; with 35+ years followup = 299 SIR men = 211, 4 cases
Gallagher [15]	PMR	320,423 deaths in British Columbia men 1950–1984	Brain and CNS	Barber and hairdresser	PMR = 69 (18–178) 4 deaths
Neuberger [3]	PMR	375 deaths from brain cancer in Missouri, 1983–1984	Brain cancer	Occupation of hairdresser or cosmetologist on death certificate	PMR = 533 (8 Obs/1.5 Exp)
Pukkala [16]	Cohort	3637 female, 168 male hairdressers in Finland	Brain and CNS cancer	Employment as hairdresser	SIR = 1.1 (0.5–2.1) in women; no brain cancer in men
Hrubec [17]	Cohort	U.S. veterans(males)	Brain cancer	Employment as barber, beautician, manicurist	RR = 1.1 (smoking adjusted; 90% CI not reported)
Lamba [18]	PMR	38,721 deaths in 24 states in U.S., 1984–1995	Brain and CNS cancer	Occupation of hairdresser or barber on death certificate	MORs: White women = 1.1 (0.9–1.3) Black women = 1.3 (0.7–2.4) White men = 1.2 (0.9–1.5) Black men = 1.3 (0.5–3.4)
Maternal exposure					
Kuijten [19]	Case–control	163 children diagnosed at 8 hospitals in PA, NJ, DE; RDD controls	Childhood astrocytic brain cancers	Mother's occupation as hairdresser: preconception pregnancy postnatal	OR = 2.5 (0.4–26.2) 1.5 (0.2–18.0) 3.0 (0.2–157.7)
Bunin [20]	Case–control	321 children aged 0–5 years diagnosed at 33 hospitals 1986–1989; 321 RDD controls	Childhood astrocytic gliomas and PNETs	Maternal use of hair coloring products in pregnancy	OR = 0.7 (0.3–1.6) astrocytic 1.1 (0.4–2.6) PNETs

Table 3. (Continued)

Author (Reference)	Design	Population	Outcome	Exposure definition	Results
Holly [21]	Case–control	539 children age <20 years, diagnosed in 3 regions in CA and WA, 1984–1991; 800 RDD controls	Primary tumor of brain, cranial nerves, cranial meninges	Maternal use of hair coloring products: the	OR ever = 1.0 (0.7–1.3)
				month before pregnancy	1.9 (0.5–7.1)
				first trimester	1.1 (0.4–3.2)
				second trimester	0.7 (0.3–1.7)
				third trimester	1.0 (0.2–5.9)

Abbreviations and symbols: CI = confidence interval; Exp = expected; Obs = observed; OR = odds ratio; PMR = proportionate mortality ratio; PNETs = primitive neuroectodermal tumors; RDD = random digit dialing; SMR = standardized mortality ratio; SIR = standardized incidence ratio; CA = California, DE = Delaware, NJ = New Jersey, PA = Pennsylvania, WA = Washington.

data on the reliability of proxy data on hair coloring product use. Deceased cases were matched to deceased controls, so misclassification due to misspecification of hair dye use by next-of-kin was likely to have been non-differential, which would result in dilution of observed risks. In fact, GBM risks based on proxies other than spouses were lower than risks based on data from spouses. Future studies with a greater proportion of self-respondents would be useful.

Previous studies of hair coloring products and brain cancer or glioma provide conflicting evidence for an association (Table 3). A two-fold risk was seen among Ontario adults with gliomas who had 'ever used hair dye or hair spray' [4], but not among men and women with astrocytic brain tumors in a small case–control in Sweden [11]. No association with brain and other CNS cancer was observed among women in the American Cancer Society cohort, who were asked about permanent hair dye use [12].

Among studies of persons with potential occupational exposure, a cohort study in Connecticut found elevated standardized incidence ratios for brain and other CNS cancer among both female and male cosmetologists, including a three-fold risk among women with longer followup [2]. A proportionate mortality study (PMR) study in Missouri identified a five-fold risk of brain cancer among hairdressers and cosmetologists [3]. Two additional studies have reported non-significantly increased PMRs for brain or brain and nervous system cancer among cosmetologists [13, 14] while four other studies considering potential occupational exposure have been negative or close to no association [15–18].

In studies of childhood astrocytomas and primitive neuroectodermal tumors (PNETs), maternal occupation as a hairdresser led to increased, but non-significant, results in one study [19], whereas maternal use of hair coloring products was not associated with risk in two others [20, 21].

Limitations of these previous studies include poor exposure assessment and broad definitions of brain cancer. Exposure status was more broadly defined or assumed in some studies (employment as a cosmetologist, use of hair dye or hair spray) than in this one, in which specific types of hair coloring products are considered. If a true association with permanent hair dyes exists, it could be masked by dilution with women exposed primarily to gradual or non-permanent hair coloring products or to no dyes at all. Second, while GBM is the most common manifestation of astrocytic brain cancer, it makes up only a subset of brain and CNS cancers, particularly among women. Associations with GBM could be missed in studies that group all brain cancers.

The International Agency for Research on Cancer (IARC) [4] has concluded that employment as hairdressers, barbers, and cosmetologists entails exposures that are probably carcinogenic, but was unable to identify the agents responsible based on epidemiologic studies. Hair dyes are complex mixtures, and formulations have changed over time. Permanent hair dyes, and darker colors in particular, contain agents known to be carcinogenic in rodent models, particularly the family of benzenediamines and other aromatic amines [4]. These agents have not been observed to cause brain tumors in experimental animals [4], but, as in humans, this tumor is rare. Brown and brunette dyes are both the most commonly reported and were associated with the highest risks in this population. In our study, the strongest associations were observed in women who dyed their hair for more than 20 years before 1985. Hair dyes were reformulated during the late 1970s and early 1980s to replace components that had been reported to be carcinogenic in animal bioassays [22]. A recent study by Zhang *et al.* [23] found an increased risk of non-Hodgkin's lymphoma only among women who used hair coloring products before 1980. The reformulation of hair dyes was suggested as a possible reason for the lack of association between hair dye use and non-Hodgkin's lymphoma among those who used dyes only in 1980 or later, although insufficient latency for disease develop-

ment may also be important. In our study, the large majority of hair dye use occurred before products were reformulated. For both gliomas and GBM, women who first began use of these products before 1980 had a greater risk than those who started use in 1980 or later, but our data were limited for drawing conclusions about differing risks by time periods. It is possible that permanent hair dyes now in use may not contain any of the agents that might have contributed to increased risk of glioma or GBM in our study.

It is not clear why GBM in particular was associated with permanent hair dyes. As GBM can be distinguished by mutational differences from lower-grade astrocytic tumors [24], one or more agents in these products might interfere with the function of a gene related specifically to GBM and not to lower grade tumors. Studies with detailed histologic, genetic, and exposure data that can evaluate this association would be useful. Future studies should also incorporate larger sample sizes, fewer proxy respondents, and the ability to evaluate the effect of changes in formulations over time.

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